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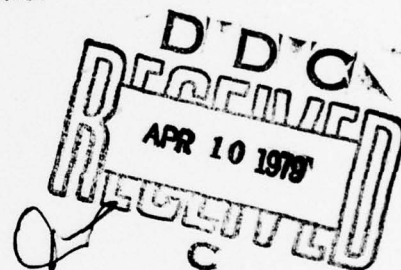
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AN AEROMEDICAL REVIEW
OF SICKLE-CELL TRAIT IN ARMY AVIATION

CLINICAL INVESTIGATION SERVICE
US ARMY AEROMEDICAL CENTER
FORT RUCKER, ALABAMA



December 1978

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER USAAMC CR-79-1	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) An Aeromedical Review of Sickie-Cell Trait In Army Aviation		5. TYPE OF REPORT & PERIOD COVERED
7. AUTHOR(s) Denniston, Joseph C., Frank S. Pettyjohn, John C. Kelliher, Edward F. Cole, and Daniel T. Sanders		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Aeromedical Center (ATZQ-AAMC) Fort Rucker, AL 36362		8. CONTRACT OR GRANT NUMBER(s)
11. CONTROLLING OFFICE NAME AND ADDRESS Clinical Investigation Service (ATZQ-AAMC-CPS) US Army Aeromedical Center Fort Rucker, AL 36362		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Headquarters (HSPA-C) US Army Health Services Command Fort Sam Houston, TX 78234		12. REPORT DATE December 1978
		13. NUMBER OF PAGES
		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) This document has been approved for public release and sale; its distribution is unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Sickle-Cell Trait Aviation Safety Aviation Physiology Hypoxia Aviators Hematology Aircrew Sudden Death		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Sickle-cell trait (HbAS) is present in approximately 8% of American black recruits and 0.05% of non-black recruits. HbAS has caused major concern in the aviation medical community as a possible causal and latent health-risk factor for aircrewmembers. Concern stems from reports purporting to show in HbAS individuals a causal relation between altitude-induced hypoxia and splenic infarction and between physical exertion at altitude and sudden death. These concerns have been offset by the lack of research establishing such a direct cause-effect relationship. In light of the prevailing controversy a literature		

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review of the aeromedical aspects of HbAS was undertaken.

The lack of proven incidents in HbAS athletes during the 1968 Olympics in Mexico City and the performance of HbAS professional football players tends to decrease the importance of existing concerns for the health and safety of HbAS individuals. The absence of definitive studies that prove or disprove a cause-effect relationship between sickle-cell trait and associated health risks would, however, support the Army's position (AR 40-501) of disqualifying HbAS individuals from flying status. The operational environment of the Army aviator poses what would appear to represent a significant potential health risk to HbAS individuals. The world-wide mission of Army aviation dictates that Army aviators will fly under a wide range of operational conditions. Missions range from nap-of-the-earth flight to those in excess of 20,000 feet in unpressurized aircraft. The reported occurrence of sickling and splenic infarction in HbAS individuals at relatively low altitudes provides additional concern for the health hazards to HbAS individuals. The problem of hypoxia may be further exaggerated or precipitated by the thermal extremes, dehydration, and the superimposed stagnant hypoxia encountered in Army aviation. The net result of these factors is the potential for circulatory stasis and resultant gross desaturation that may precipitate sickling, crisis, or infarction.

In light of such risks, even though controversial and tenuous, the question of cause-effect relationship must be resolved without sacrifice of aviation safety or medical risk to the individual. In actual aeromedical practice, the medical ethics of protecting the individual in consonance with protection of the high tax dollar investment in training and operational readiness of the US Army aviator dictates a conservative posture at this time. Definitive research studies are indicated to fully define the aeromedical risk, if any, of HbAS.

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9 14 USAAMC-CR-79-1
USAAMC CLINICAL REPORT (NO. 79-1)

6 An Aeromedical Review
of Sickle-Cell Trait in Army Aviation.

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SUMMARY

The US Army Aeromedical Center has the Department of the Army worldwide mission of reviewing all flight medical examinations involving aviators, flight crewmembers, and air traffic control personnel. This mission requires the aeromedical evaluation of a wide range of clinical entities. This clinical report represents an initial review of the aeromedical risk of sickle-cell trait in Army aviation.

Sickle-cell trait is considered a controversial aeromedical risk. It becomes even more difficult to assess in light of the operational employment of US Army aviators in a wide range of flight profiles from high altitude to nap-of-the-earth operational missions. Currently, individuals with sickle-cell trait are considered possible medical risks as well as aviation safety risks.

This study reviews the question of aeromedical risk and defines the need for further research studies to fully evaluate the cause-effect relationship of altitude-induced hypoxia, sudden death, and splenic infarction in sickle-cell trait carriers. The data retrieval system of the US Army Aeromedical Center Data Repository could be utilized to follow the natural history of military personnel with sickle-cell trait. Clinical evaluation of sickle-cell trait from an aviation medicine perspective will be a continuing goal of the US Army Aeromedical Center in order to provide a sound basis for revision and development of US Army regulations.

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ABSTRACT

Sickle-cell trait (HbAS) is present in approximately 8% of American black recruits and 0.05% of non-black recruits. HbAS has caused major concern in the aviation medical community as a possible causal and latent health-risk factor for aircrewmembers. Concern stems from reports purporting to show in HbAS individuals a causal relation between altitude-induced hypoxia and splenic infarction and between physical exertion at altitude and sudden death. These concerns have been offset by the lack of research establishing such a direct cause-effect relationship. In light of the prevailing controversy a literature review of the aeromedical aspects of HbAS was undertaken.

The lack of proven incidents in HbAS athletes during the 1968 Olympics in Mexico City and the performance of HbAS professional football players tends to decrease the importance of existing concerns for the health and safety of HbAS individuals. The absence of definitive studies that prove or disprove a cause-effect relationship between sickle-cell trait and associated health risks would, however, support the Army's position (AR 40-501) of disqualifying HbAS individuals from flying status. The operational environment of the Army aviator poses what would appear to represent a significant potential health risk to HbAS individuals. The world-wide mission of Army aviation dictates that Army aviators will fly under a wide range of operational conditions. Missions range from nap-of-the-earth flight to those in excess of 20,000 feet in unpressurized aircraft. The reported occurrence of sickling and splenic infarction in HbAS individuals at relatively low altitudes provides additional concern for the health hazards to HbAS individuals. The problem of hypoxia may be further exaggerated or precipitated by the thermal extremes, dehydration, and the superimposed stagnant hypoxia encountered in Army aviation. The net result of these factors is the potential for circulatory stasis and resultant gross desaturation that may precipitate sickling, crisis, or infarction.

In light of such risks, even though controversial and tenuous, the question of cause-effect relationship must be resolved without sacrifice of aviation safety or medical risk to the individual. In actual aeromedical practice, the medical ethics of protecting the individual in consonance with protection of the high tax dollar investment in training and operational readiness of the US Army aviator dictates a conservative posture at this time. Definitive research studies are indicated to fully define the aeromedical risk, if any, of HbAS.

ACKNOWLEDGEMENTS

The authors are indebted to Mesdames Judy Holmes and Carolyn Benton for preparation of this report, and Mesdames Audrey Neal, Sarah Linton, and Jeanette Chambers for assistance with the literature review.

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AN AEROMEDICAL REVIEW OF SICKLE-CELL TRAIT IN ARMY AVIATION

INTRODUCTION

The phrase "sickle-cell trait" refers to a specific heterozygous hemoglobinopathy (HbAS) in which individuals inherit one normal hemoglobin (A) gene and one abnormal hemoglobin (S) gene. The red blood cells of these individuals contain both HbA and HbS, the ratio of which is dependent on the individual production rates of HbA and HbS rather than on the selective destruction of a specific Hb. The HbS of sickle-cell trait usually will constitute 35 to 45% (34) of the total Hb. Sickle-cell trait is present in approximately 8% (33) of American black recruits and 0.046% (19) of the nonblack recruits.

Although HbAS is considered a benign entity by many, it has caused major concern in the aviation medical community as a possible causal and latent health-risk factor for aircrewmembers. This caution and concern stems predominantly from the multitude of reports purporting to show a causal relationship between altitude-induced hypoxia and the occurrence of splenic infarction in individuals with HbAS. Most recently, this concern has been heightened by reports of sudden deaths in HbAS recruits at modest altitude during physical exertion. These concerns, however, have been weakened by the failure to establish a cause-effect relationship between HbAS and splenic infarction or sudden death in any of the reported cases. The complete absence of HbAS associated "mishaps" among HbAS athletes during the 1968 Olympics in Mexico City (7,349 feet) and the well-established normal performance of HbAS professional football players, often playing at altitudes above 5,000 feet, tends to further decrease the importance of existing concerns for the health and safety of HbAS individuals.

The purpose of this review is to evaluate the scientific literature of HbAS, consider current views of sickle-cell trait with regard to Army aviation, and provide recommendations regarding future research.

REVIEW

The first in-depth review of sickle-cell trait was conducted by the National Academy of Sciences-National Research Council (NAS-NRC) in 1973 (34). This study was prompted by a Department of Defense request for assistance in establishing rational and medically sound guidelines for the screening, management, and disposition of the sickle-cell trait carrier in the Armed Forces. Importantly, this Ad Hoc Committee was unable to establish

any scientific basis for excluding HbAS individuals from the Armed Forces or limiting their activities or duties. However, in the absence of conclusive scientific evidence to the contrary, the Committee recommended that HbAS individuals be excluded from duty as pilots or co-pilots:

Except for pilots and co-pilots persons with sickle-cell trait should not be restricted from flight duty...

The Committee's findings and subsequent recommendation, at first glance, seem somewhat paradoxical. In all probability, this cautious position resulted in part from the disconcerting report of sudden death in four black soldiers undergoing basic training at 4,060 feet above sea level (16) and the Committee's responsible concern with assuring the health and safety of HbAS service personnel under all military operational environments. This was evident from the Committee's proposal for further study and is evidenced in the following statement by the NAS-NRC Committee.

This study, if properly performed, would yield data that might provide a firm medical and scientific basis to guide the development or revision of Armed Forces regulations.

Obviously, the proposed study kept the issue open and subject to change pending conclusive research studies.

In 1974 a seminar was held, "Sickle-Cell Anaemia and Aviation", in Dakar under the auspices of the African Civil Aviation Commission (31). A principle reason for conducting this meeting was to review objectively the reasons why some countries exclude HbAS individuals from flight status. This Commission concluded that sickle-cell trait alone should not be the basis for disqualifying an individual from flying duties. This conclusion was based, in part, on the apparent absence of HbAS associated problems in African pilots flying both pressurized and unpressurized aircraft at various "normal" operational altitudes and the lack of scientific data demonstrating a solid correlation between sickle-cell trait and incidents of incapacitation or sudden death. Further, the report concludes:

...the sickle-cell trait individual presents no greater health hazard than the HbAA individual in the aviation environment.

The first published attempt at resolving the conflicting reports on hypoxia and sickle-cell trait appeared in 1976 (20). The pertinent conclusion of this detailed and excellent review was that the presence

of sickle-cell trait is not, of itself, a basis for the aeromedical disqualification of an individual from flying status. Despite this seemingly tenacious conclusion, the author vacillates and confuses the issue by stating:

Physiological training, especially in the use of oxygen equipment, is of great potential usefulness to the airman with sickle trait. A hypoxic experience is not necessary for this training and should be avoided. Trainees of SA genotype should, however, be encouraged to observe hypoxic signs in other trainees...

The enigma of these statements is obvious. If there is no scientific or medical basis for disqualifying HbAS individuals from flight status it would follow that there is no reason to exclude these same individuals from required hypoxic training under carefully controlled conditions in a hypobaric chamber. Chamber flights afford trainees the opportunity to experience and identify their individual signs and symptoms of hypoxia under safe and controlled conditions. Elimination of such training invites disaster in the operational aviation environment.

The author's staunch position is further enervated in the appendix of the review where Dr. R. Fisher, Chief Medical Examiner for the State of Maryland, concludes:

I am sufficiently convinced that I would advise any AS hemoglobin individual to avoid hypoxic anesthesia as well as alcohol or drug abuse, or any other situation in which there might be an episode of hypotension or hypoxia, lest an otherwise survivable lesion be suddenly converted to a fatal process.

This conclusion expresses genuine concern for the health of individuals with sickle-cell trait and although it contrasts with the author's conclusion it is consistent with his recommendation to waive the hypoxia training of HbAS individuals.

Although the above review (20) provides convincing evidence and documentation that there is no cause-effect relationship between HbAS and altitude complications/intolerance, it does suggest that HbAS may be an important factor in delaying recovery from altitude-induced unconsciousness. This has serious implications with regard to high-altitude missions where hypoxia represents a constant environmental threat. In terms of hypoxic-induced sickling and resulting vaso-occlusive disease one must consider the P_{O_2} in the microcirculation,

with the venous P_{O_2} (P_{vO_2}) considered the limiting factor. Extensive in vitro studies (10,11) indicate that sickling of HbAS cells does not occur usually until the P_{O_2} is ≥ 15 mm Hg. Relating this to an approximate altitude is not simple since the effluent P_{vO_2} will depend on a multitude of factors, not the least of which is the vascular bed from which the blood is returning. Tissues with a relative high oxygen extraction such as the brain, heart, and muscle would probably represent potential sickling sites under hypoxic conditions. For example, the femoral P_{vO_2} at 13,000 feet has been reported to be 20 ± 1 mm Hg at rest and 16 ± 0.7 mm Hg with mild exercise in normal subjects (12). These P_{vO_2} values approximate those required to induce sickling in HbAS preparations.

The concentration of HbS and the pH represent two additional factors that must be considered in the sickling phenomenon. In general, the higher the HbS concentration and the lower the pH the greater percentage of sickling and the higher the P_{vO_2} at which sickling will occur (6,9). Hypoxia, acidosis, dehydration, and high concentrations of HbS are the usual factors considered key to tactoid formation (16). These in vitro data strongly suggest that sickling could be a serious problem in HbAS individuals at relatively modest altitudes; however, in vivo sickling and trapping of sickled erythrocytes have not been demonstrated at an equivalent altitude of 18,000 feet (10% O_2) as evidenced by the lack of disappearance in rats of chromium labeled red blood cells from individuals with sickle cell trait (4,27). This finding contrasts not only with the in vitro data but also with the observation of sickling following six minutes exposure of a Caucasian with sickle-cell trait to a simulated altitude of 10,000 feet in a hypobaric chamber (35). This latter finding is inconsistent with the lack of evidence of sickling in HbAS cadets exposed to a simulated altitude of 16,000 feet in a hypobaric chamber (14).

These differences point out an apparent individual variability that exists with regard to hypoxic-induced sickling with HbAS. It further suggests that within the population of individuals with sickle-cell trait there may exist a small subgroup at serious risk. Although identification of this risk subgroup remains elusive at this time, it is recognized that HbAS individuals with high percentages of HbS are more susceptible to sickling since the degree of hypoxia required to cause sickling depends, in part, on the proportion of HbS present (6,7,9,10). In this regard, in vitro studies suggest that HbAS individuals with high concentrations of HbS have a risk of sickling that differs little from that in patients with sickle-cell disease (15). The relative importance of the concentration of HbS is further emphasized by evidence suggesting that sudden death due to primary sickling in the non-anemic individual would be unlikely in sickle-cell states with less than 40% HbS (26).

In a recent review of the health risks of sickle-cell trait convincing evidence was presented demonstrating that hyposthenuria, renal hematuria, bacteriuria and pyelonephritis in pregnancy, and splenic infarction with high altitude hypoxia occurs with increased frequency in sickle-cell trait individuals (30). Certain facts need to be reviewed in regard to these findings.

Hematuria is reportedly so rare in individuals with sickle-cell trait that causes other than HbAS should be considered in making the diagnosis (8,13). Thus, its importance as a risk factor must be viewed with some skepticism. Hyposthenuria, on the other hand, although rarely considered a problem in HbAS individuals (34), may have some significance since the kidney might represent an important site for the initiation of sickle crisis in dehydrated individuals with sickle-cell trait (20). Further, the renal concentrating ability in HbAS individuals decreases with age (32) and could pose a potential problem in the combat environment where adequate hydration is difficult to maintain. Despite such speculation, the evidence to date suggests that dehydration would not be exaggerated in HbAS individuals (2). Conclusive studies, however, have not been conducted to evaluate this potential risk.

With regard to hypoxic-induced splenic infarction, it has been argued that most reported cases of splenic infarction at altitude may actually have occurred in individuals with doubly heterozygous sickle-cell hemoglobinopathies rather than sickle-cell trait (3). Interestingly, it has been reported that the association of objectively documented splenic infarction in persons with electrophoretically proven sickle-cell trait has only occurred in four cases, and two of these patients were white, implying a greater frequency in Caucasians with sickle-cell trait (5). The importance of the occurrence of splenic infarction at altitudes as low as 2,500 feet (25) and even under apparently non-hypoxic conditions (18) cannot be ignored. A predisposition to splenic infarction has been suggested in individuals with a high percentage (>42%) of HbS (29).

The report of four cases of sudden death attributable to sickle-cell trait among 4,000 black soldiers undergoing basic training at 4,060 feet above sea level (16) prompted the Department of Defense to seek clarification (34) of the health risks, if any, of sickle-cell trait. The Ad Hoc Committee of the National Academy of Sciences-National Research Council viewed the report as circumstantial with no evidence of a cause-effect relationship. Considering that 7 to 9 percent of drafted Negroes have trait, 280 to 360 of the above recruits involved were at risk. With four recorded deaths the mortality rate was in excess of 1 percent (22). Obviously, as suggested in that report, a 1 percent death rate in this group from basic training alone would

provide the basis for exclusion from the military service. The investigators who initially reported the sudden deaths conducted a follow-up prospective study of 1,000 black recruits (1) that included 73 individuals with sickle-cell trait. These recruits were subjected to the same stress and environment as reported in their earlier study of sudden death and no morbidity was noted. However, as is apparent from their previous data (2) only a maximum of one incident would have been anticipated to occur in their prospective study. Despite the apparent lack of conclusive evidence establishing a firm relationship between sudden death and sickle-cell trait, clinical concern continues to exist. For example, it has been reemphasized recently that massive sickle cell anemia may occur in HbAS individuals, and that this may lead to sudden death under certain pathophysiologic conditions such as acidosis, dehydration, hypothermia, and hypoxia (21).

If altitude and/or exercise precipitated problems in individuals with sickle-cell trait, one could ponder the reported ability of blacks with sickle-cell trait to participate without problem in physically demanding sports such as professional football (23). It was noted in this latter study that one of the National Football League teams played over half of its games at an altitude in excess of 5,000 feet and that the team physicians were unaware of any problems relating to the trait. Similarly, sickle-cell trait problems were not encountered among blacks in the 1968 Olympic Games in Mexico City at an altitude above 7,000 feet (28). It is suggested that intensive training may have conditioned these athletes so that they adapted to the stress of hypoxia during the strenuous activity of the Olympic Games (17). The apparent lack of trait associated problems in these studies is consistent with earlier observations. From a population of 1,500 black cadets in training at Tuskegee Army Airfield from 1941 to 1943, no eliminations from the flight instruction occurred as a result of problems arising from sickle-cell trait (14). Further, the African Civil Aviation Commission (31) has indicated that incidents of HbAS associated problems in African pilots flying both pressurized and unpressurized aircraft are reportedly rare, if they occur at all.

Despite the lack of evidence supporting a causal relationship between HbAS and serious health risks, the aeromedical reviewer is plagued by the multitude of reports purporting such a relationship. Further, one might question the number of incidents that have occurred but have not been reported in the literature as many physicians can recall an anecdotal "case" in which sickle-cell trait was implicated in cardiac conditions and/or sudden death.

CONCLUSION

Review of the foregoing material leads to the inescapable conclusion that sickle-cell trait is viewed quite differently today than it was in

the late 1960's and early 1970's. Sickle-cell trait does not have the stigma it once did, and many consider it a relatively benign entity. In fact, it is believed that the most important implication of sickle-cell trait is a genetic one (24). Despite this changing attitude there can be little doubt that controversy still exists even though statistical data linking a cause-effect relationship to sickle-cell trait is lacking (20,30). This position has been summarized appropriately (30):

Case reports and clinical anecdotes have served a useful purpose in pointing up the possibility of meaningful associations, but they do not prove that associations are other than chance.

What is obvious, however, is that prospective research studies are woefully lacking. Reconsideration of the NAS-NRC recommendation to disqualify pilots and co-pilots having sickle-cell trait leads to the conclusion that this recommendation may have resulted, in part, from the assumption that the Department of Defense would carry out the National Research Council's proposed study to provide the medical and scientific basis for guiding the development and/or revision of the Armed Forces regulations with regard to the S-hemoglobinopathies. Such a study has not been done, leaving open the question of "critical risk subgroup" identification within the sickle-cell trait population. One study was proposed within the US Army Medical Research and Development Command, but was rejected by Human Use considerations. The problem of risk could be partially circumvented and answered by using acceptable animal models for preliminary, yet, detailed investigative studies.

In the absence of definitive studies that prove or disprove a cause-effect relationship between sickle-cell trait and associated health risks the Army's position (AR 40-501) of disqualifying HbAS individuals from flying status is not unreasonable. The operational environment of the Army aviator poses what would appear to represent a significant potential high health risk to HbAS individuals. The world-wide mission of Army aviation dictates that Army aviators will fly under all operational conditions. Missions in excess of 20,000 feet in unpressurized aircraft are identified. The reported occurrence of sickling and splenic infarction in HbAS individuals below these altitudes provides additional concern for the health hazards to HbAS individuals. The problem of hypoxia may be further exaggerated or precipitated by the thermal extremes, dehydration, and the superimposed stagnant hypoxia encountered in Army aviation. This latter situation can occur with mild to moderate G-forces and with missions necessitating long periods of relative immobilization.

The net result of these factors is, of course, the potential for circulatory stasis and resultant gross desaturation that may precipitate sickling, crisis, or infarction. In light of such a risk, even though controversial and tenuous, the question of cause-effect relationship must

be resolved without sacrifice of aviation safety or medical risk to the individual. In actual aeromedical practice, the medical ethics of protecting the individual in consonance with protection of the high tax dollar investment in training and operational readiness of the US Army aviator dictates a conservative posture at this time.

RECOMMENDATIONS

1. A study group should be appointed to review and evaluate immediately all the current scientific literature on sickle-cell trait as it impacts on Army aviation.
2. Emphasis and priority should be given to establishing an immediate and detailed research study to define the health hazards of sickle-cell trait, if any.
3. The US Army Aeromedical Center's Data Repository should be utilized to provide long-term evaluation of any correlation between sickle-cell trait and health risk.

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AMC CR-79-1
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ARMY AVIATION by Joseph C. Bennett, M.D., M.C.
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2. Aviation Safety
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stems from reports purporting to show in HbAS individuals a causal relation between alti-
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sudden death. These concerns have been offset by the lack of research establishing such
a direct cause-effect relationship. In light of the prevailing controversy a literature
review of the aeromedical aspects of HbAS was undertaken.

The lack of proven incidents in HbAS athletes during the 1968 Olympics in Mexico City and
the performance of HbAS professional football players tends to decrease the importance of
existing concerns for the health and safety of HbAS individuals. The absence of defini-
tive research studies are indicated to fully define the aeromedical risk, if any, of HbAS.
In light of such risks, even though controversial and tenuous, the question of cause-
effect relationship must be resolved without sacrifice of aviation safety or medical risk
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